
NMI SUMMIT 2024
An event by:
Nutritional Medicine Institute

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NMI SUMMIT 2024
An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, & Healthy Ageing
11-12 October 2024
Featuring Professor Nick Lane, Dr. Iain Hargreaves, Dr. Joseph Pizzorno, Dr. Nina Fuller-Shavel, Dr. Deanna Minich, Lorraine Nicolle, Claire Sehinson, Professor Robert Thomas and Benjamin Brown
An event by:
Nutritional Medicine Institute
Platinum sponsors:
regenerus labs
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An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing

Keynote Speaker

Professor Nick Lane

Mitochondria and the Meaning of Life

9:45-10:30am

An event by: Nutritional Medicine Institute

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Mitochondria

and the meaning of life

Nick Lane
Professor of Evolutionary Biochemistry
University College London

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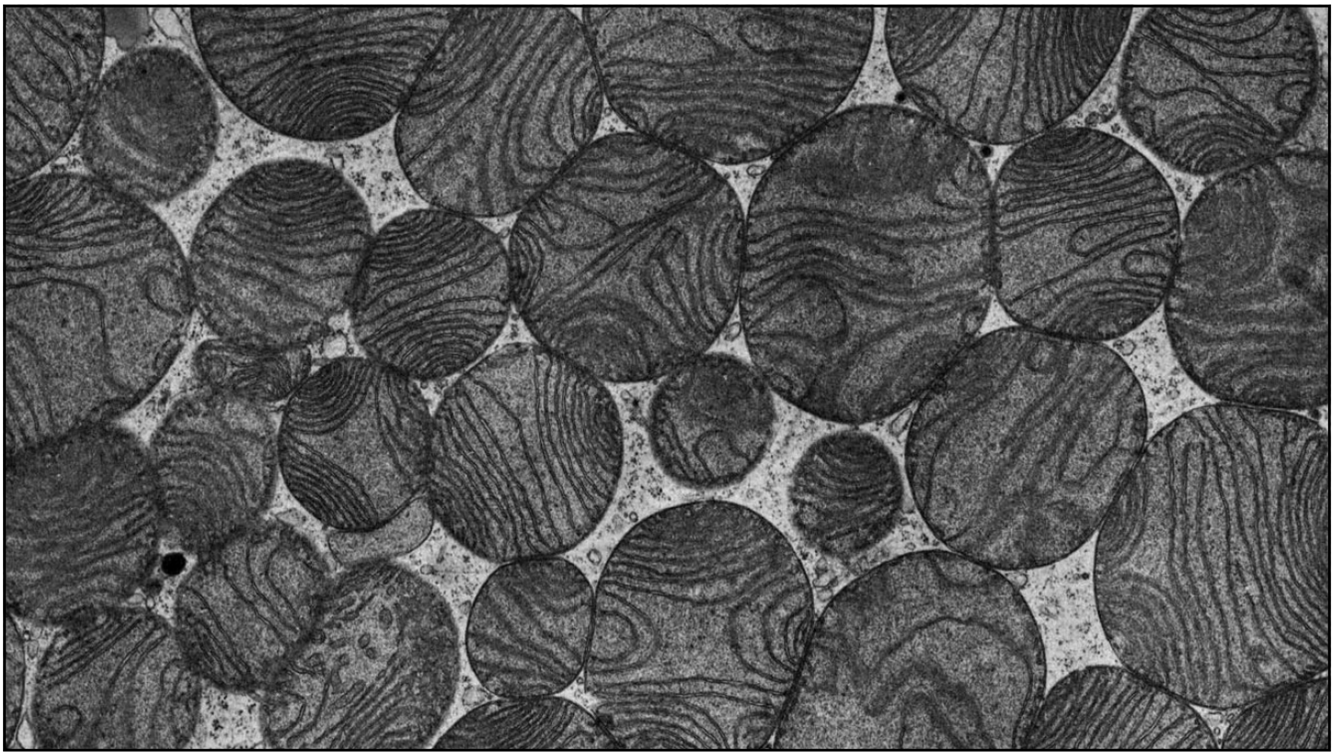

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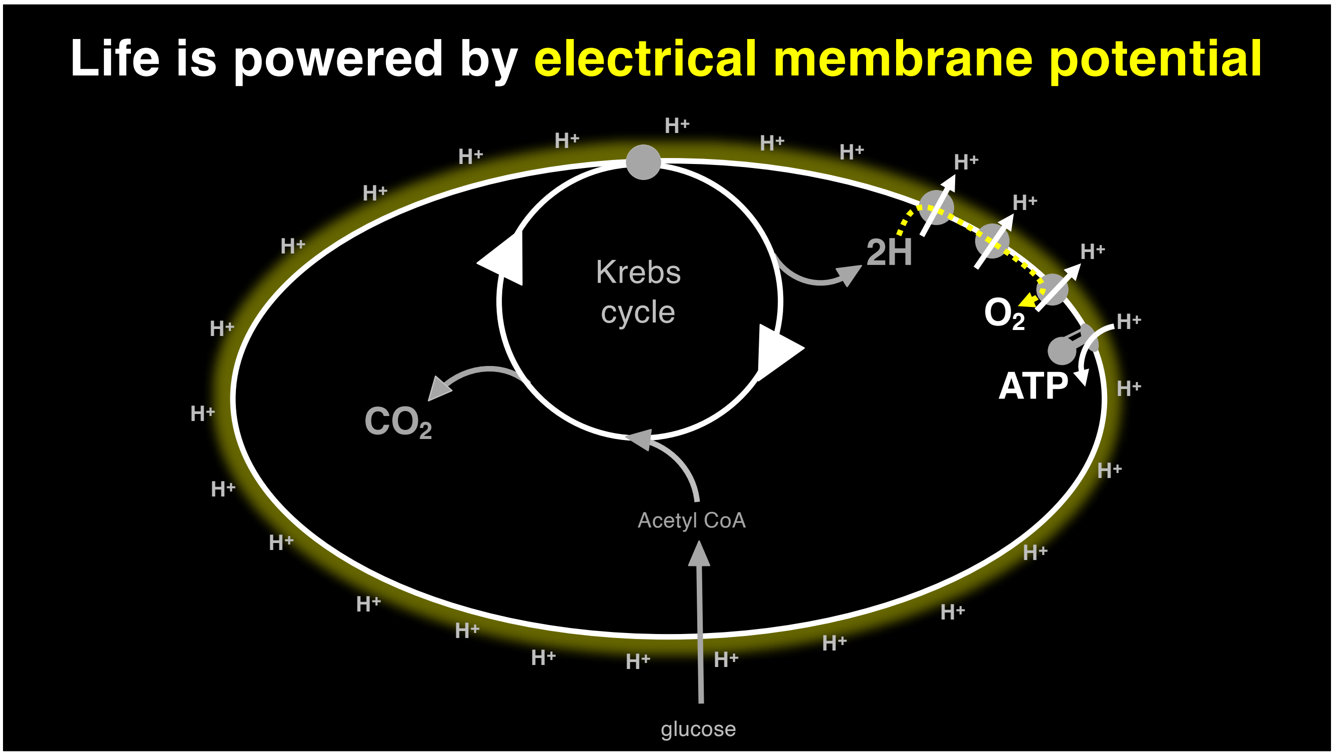
Life is powered by electrical membrane potential
Krebs cycle
2H
O_2
ATP
CO_2
Acetyl CoA
glucose
H^+

6

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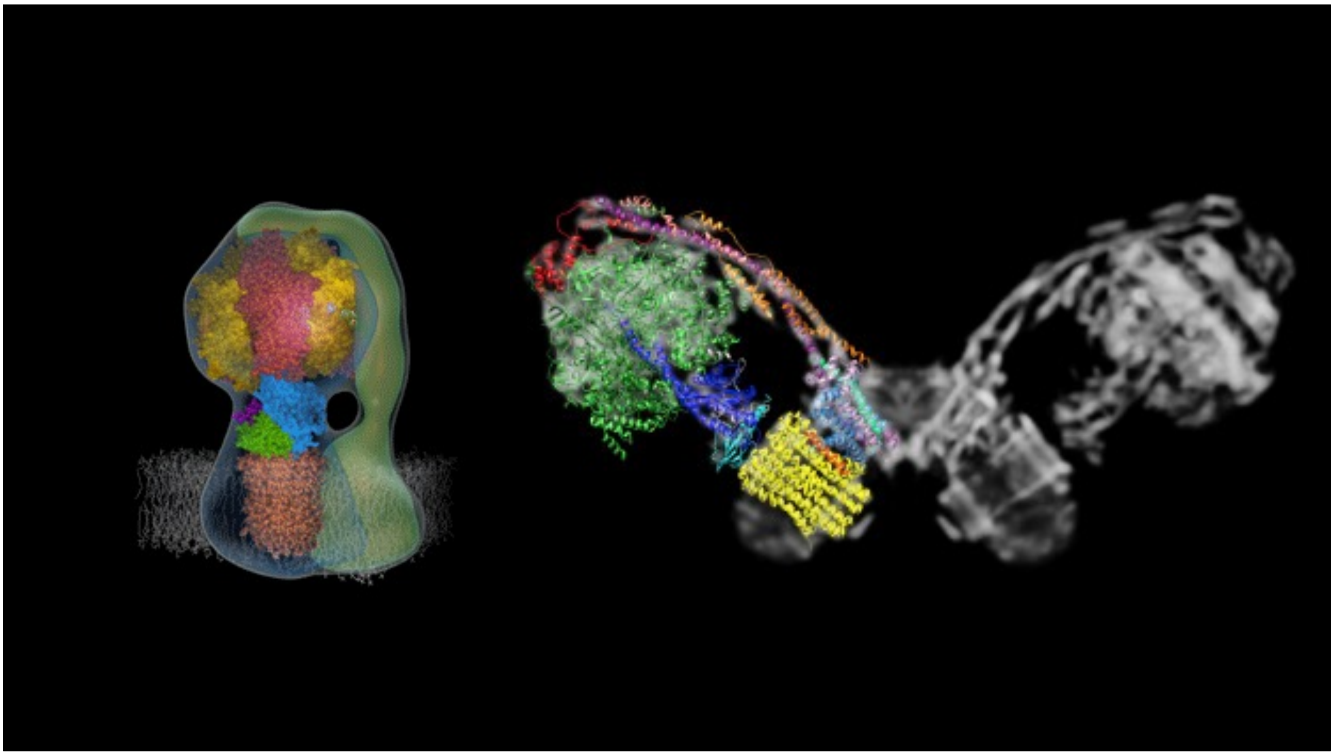

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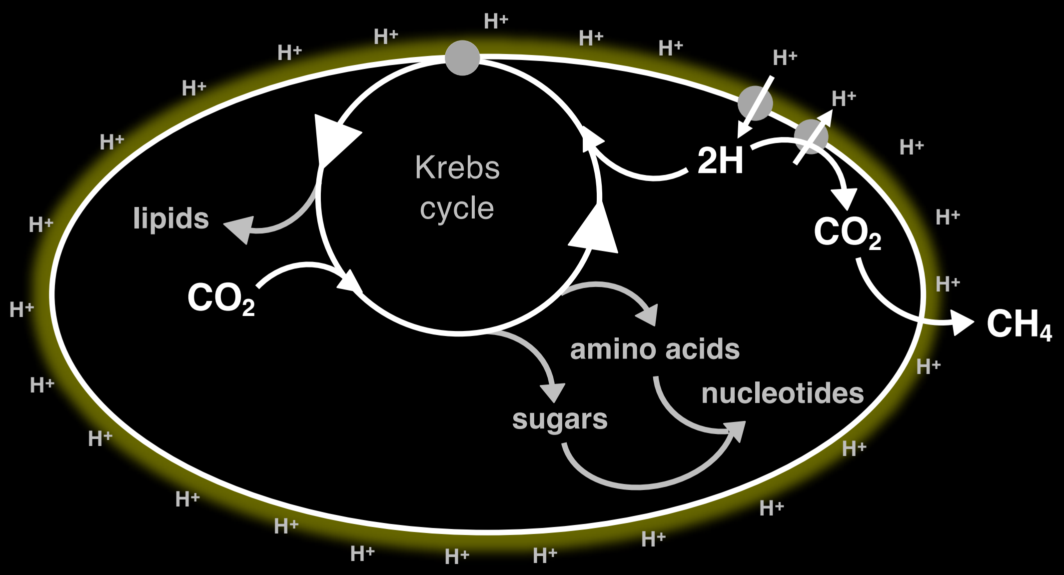
Electrical membrane potential drives growth



The reverse Krebs cycle fixes CO_2 to make organic molecules – it is the heart of metabolism

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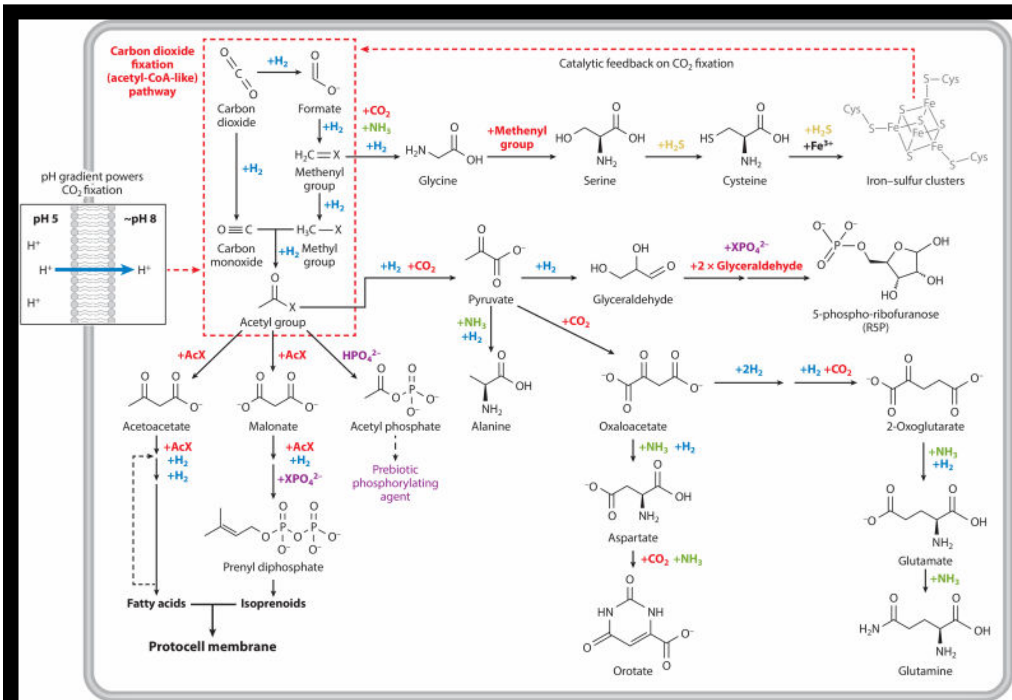


The

chemistry

of

life

is

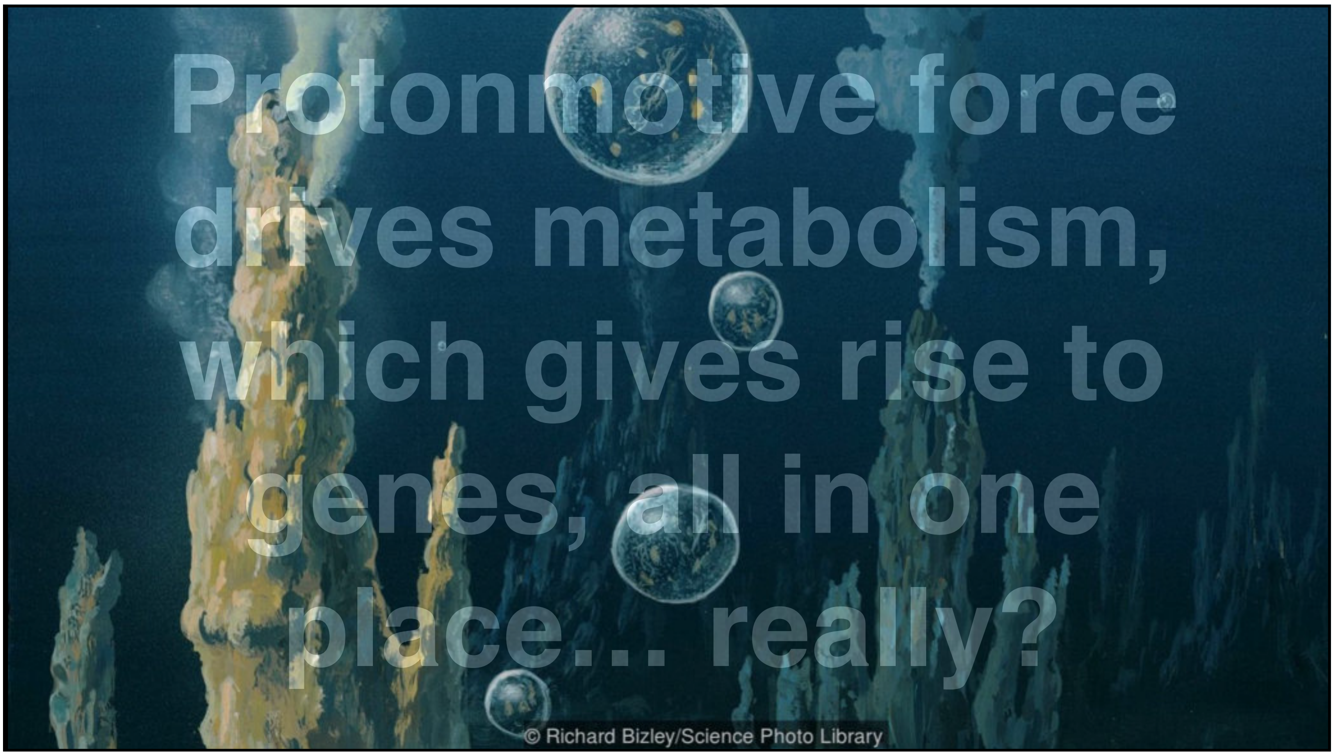
older

than

genes

Harrison S & Lane N. Life as a guide to prebiotic nucleotide synthesis. *Nature Commun* 9, 5176 (2018)

10


Protonmotive force drives metabolism, which gives rise to genes, all in one place… really?
© Richard Bizley/Science Photo Library

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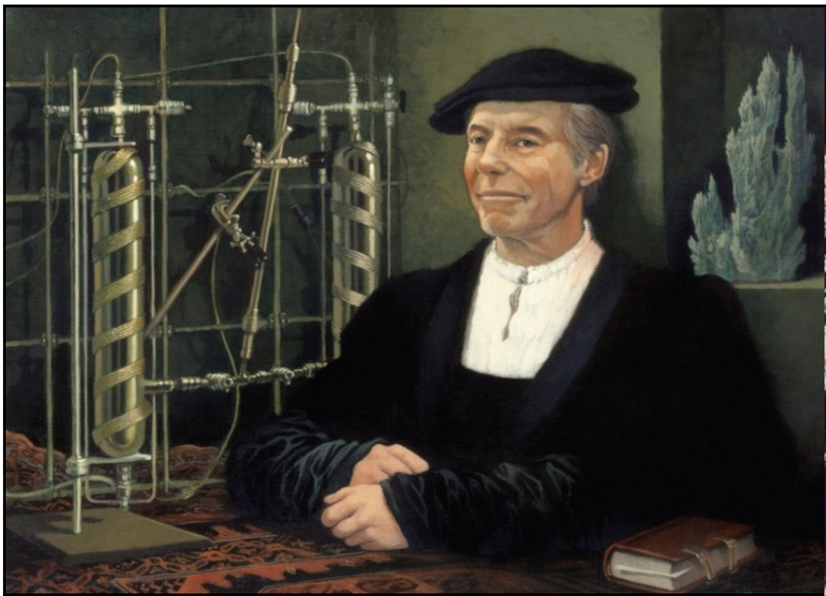
Alkaline hydrothermal vents
Deborah Kelley
Lost City vent field

12



Mike Russell, Nascence Man

High concentrations of H_2 and CO_2
Proton gradients across catalytic FeS walls

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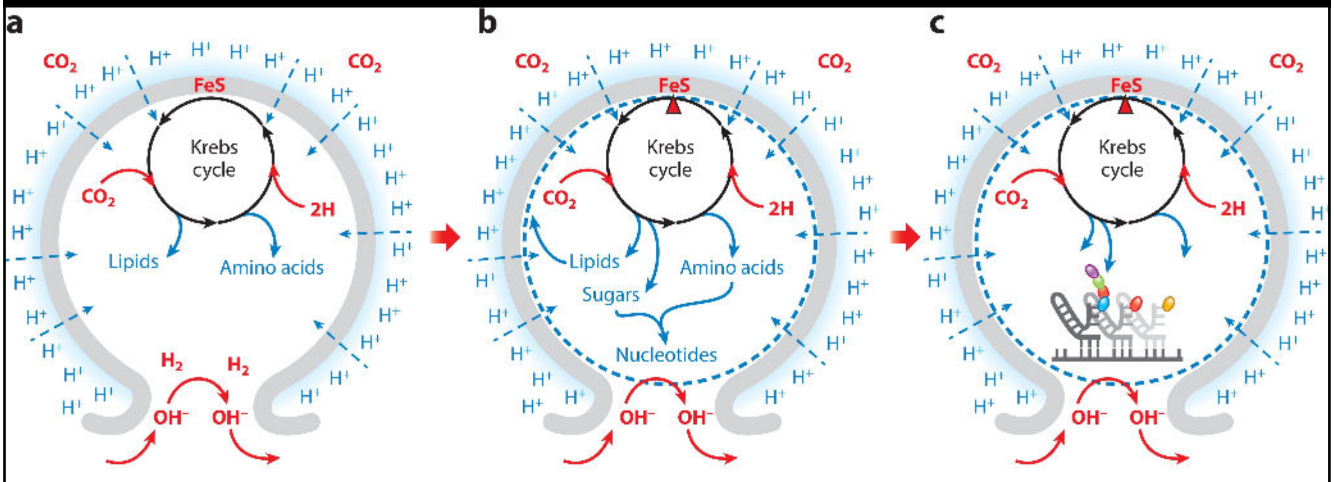
Hypothesis: converting gases into growing cells



Proton flux drives reaction between H_2 and CO_2 to form protocells in alkaline pores → metabolism, growth and emergence of genes

Harrison SA, Rammu H, Liu F, Halpern A, Nunes Palmeira R, Lane N.
Life as a guide to its own origins. *Annual Review of Ecology, Evolution & Systematics.* 54: 327–50 (2023)

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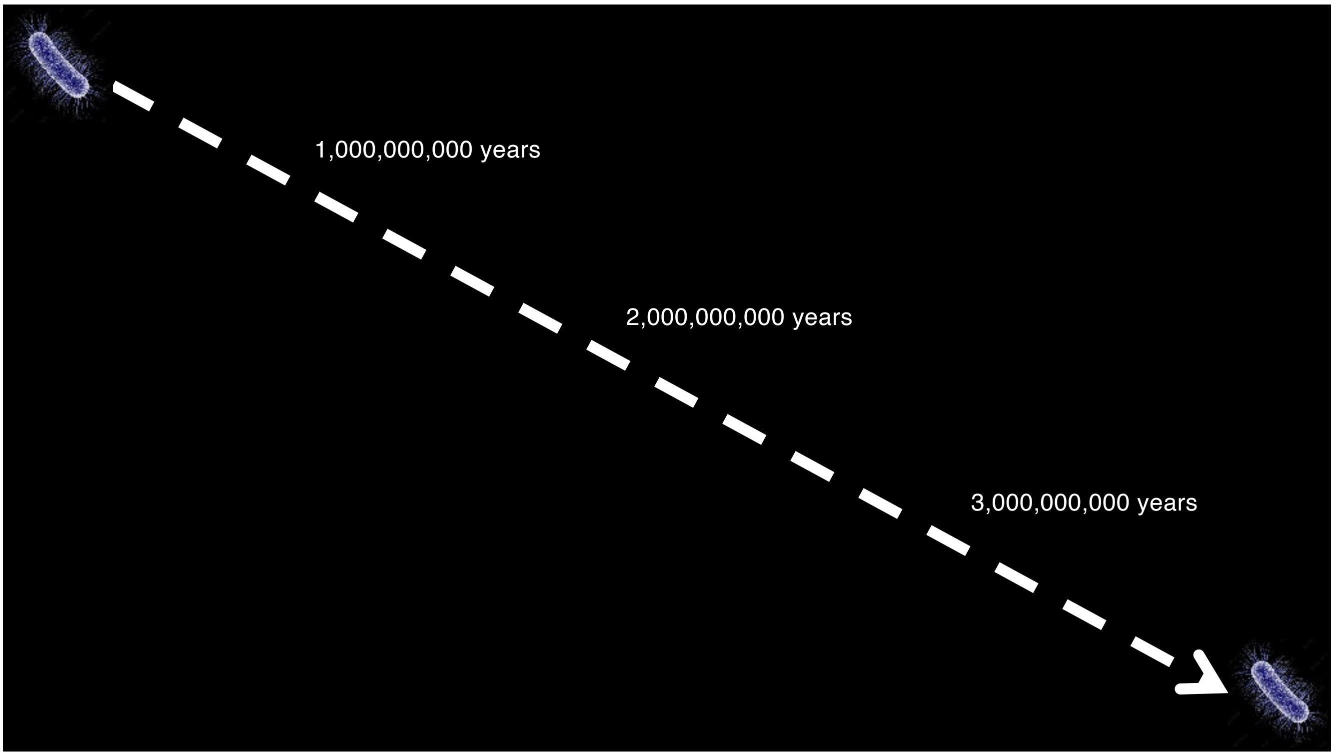
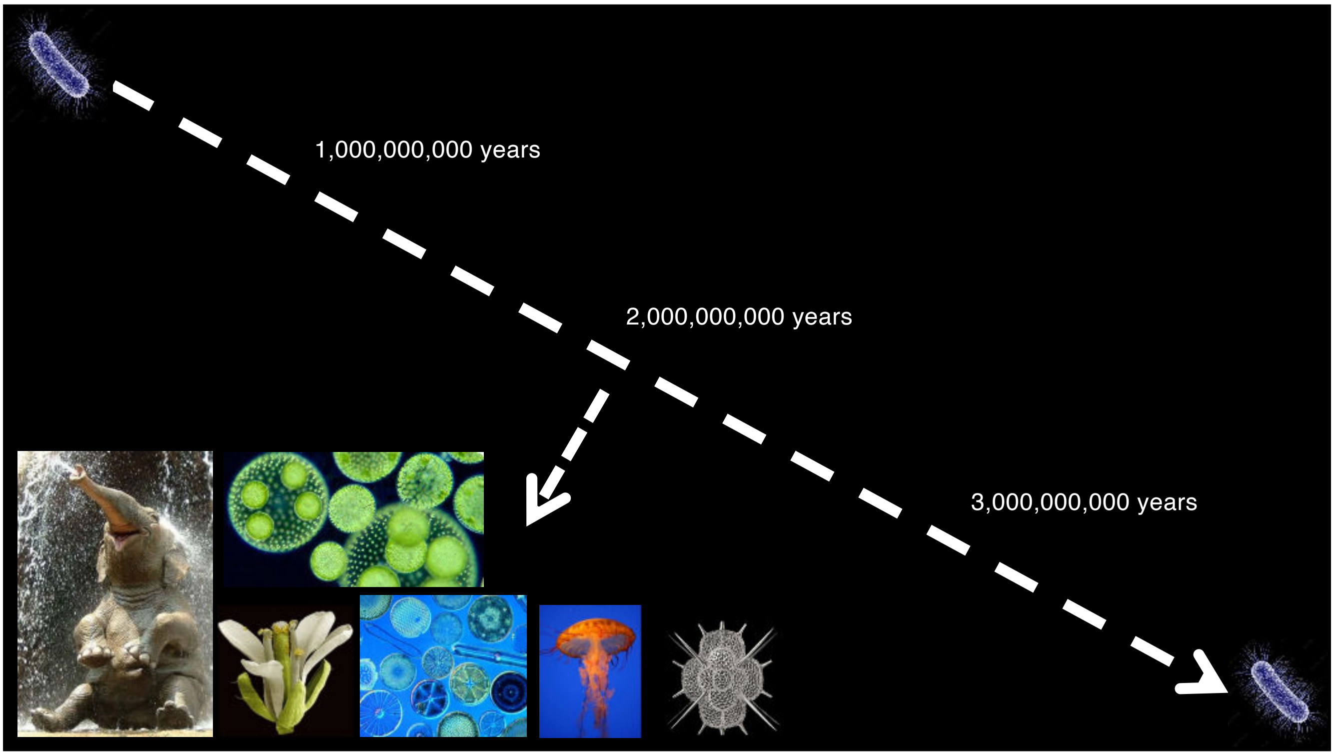

1,000,000,000 years
2,000,000,000 years
3,000,000,000 years

15


1,000,000,000 years
2,000,000,000 years
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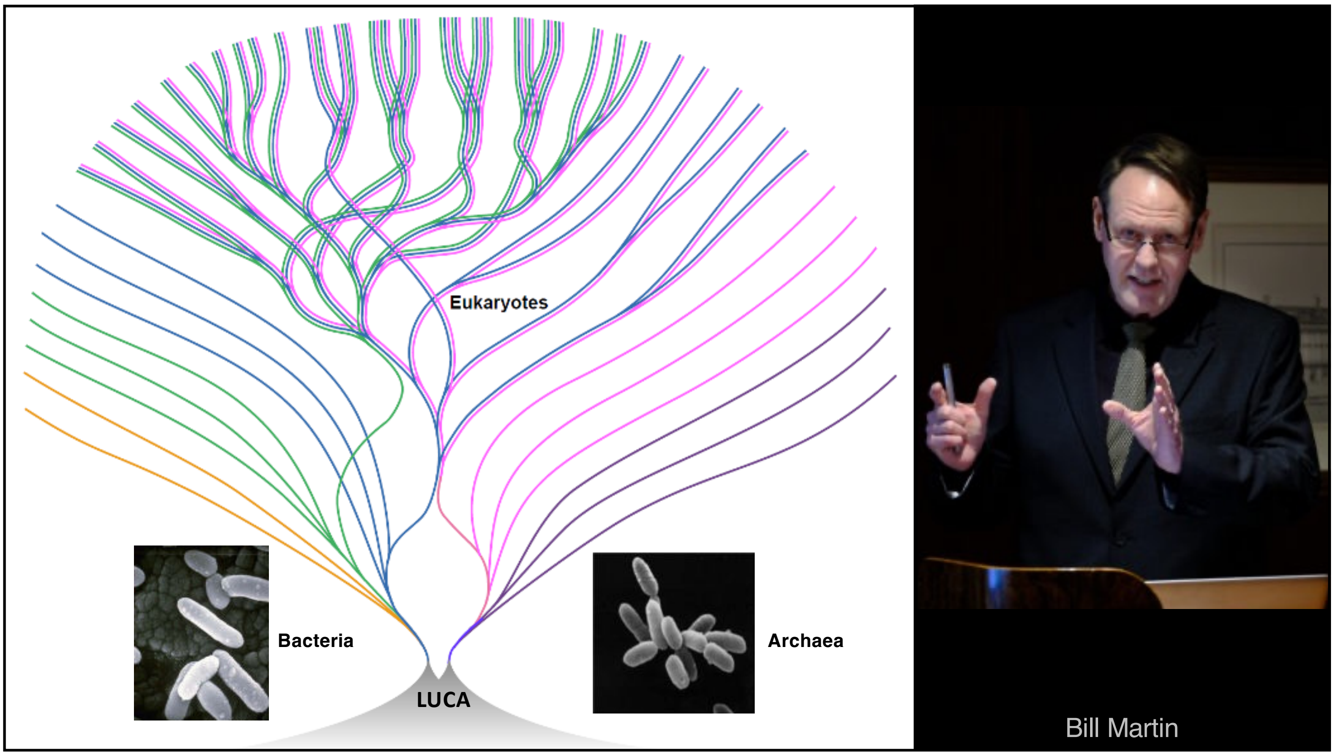
16



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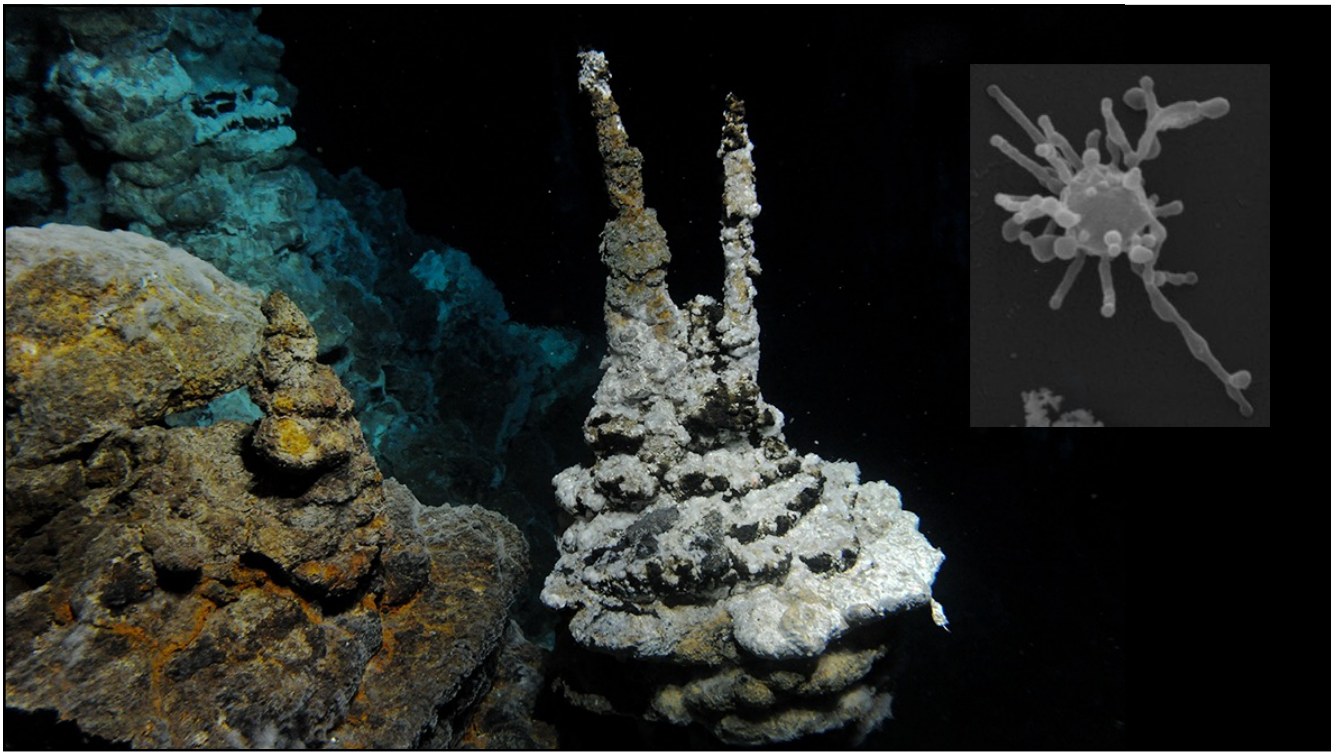

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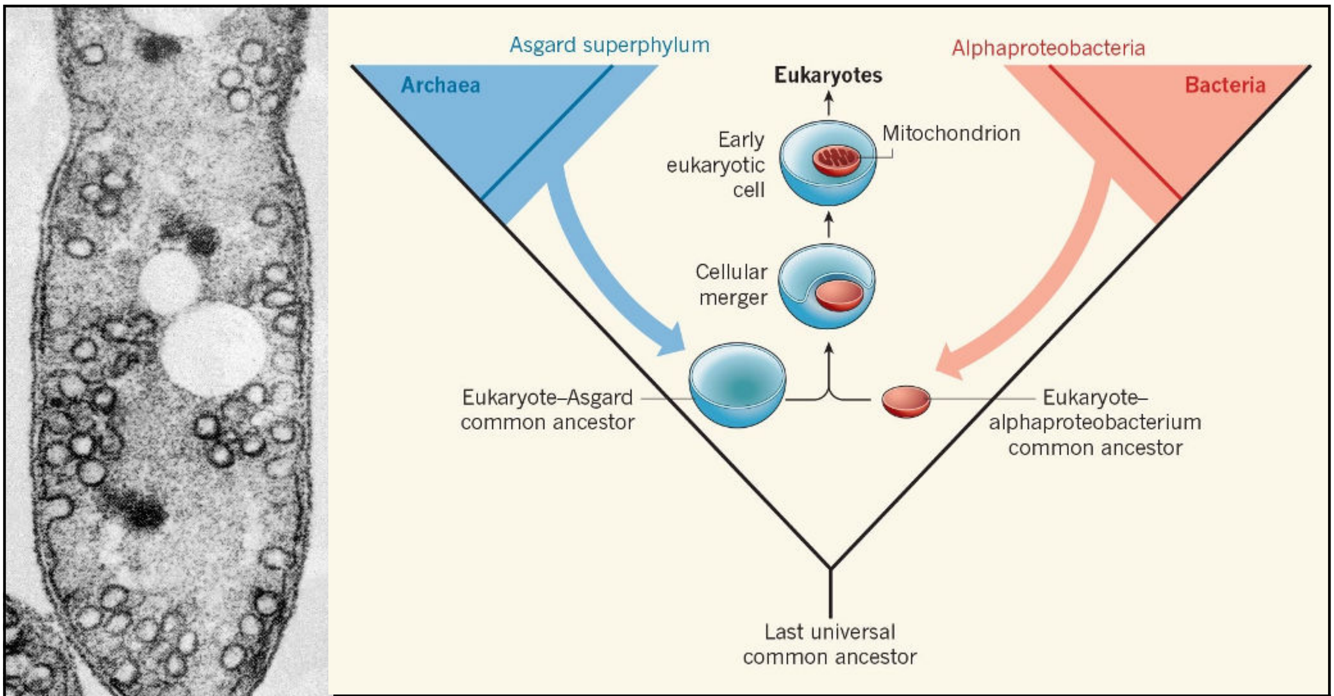

McInerney JO, O'Connell MJ. Microbiology: Mind the gaps in cellular evolution. *Nature* 541: 297-299 (2017)

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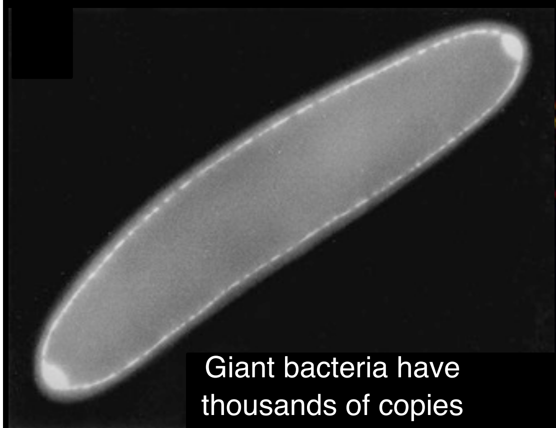
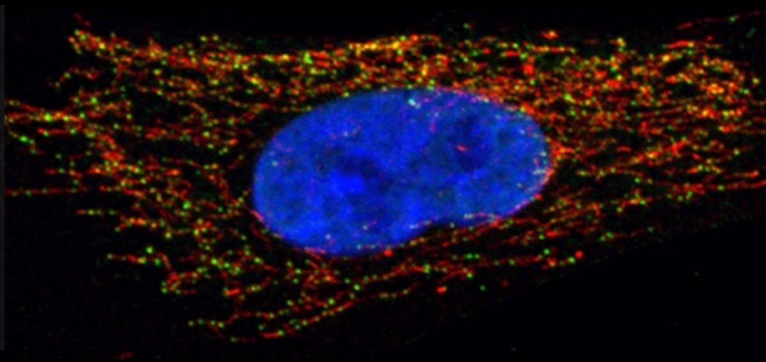
Eukaryotes: multi-bacteria power without the overheads



Giant bacteria have thousands of copies of their complete genome



Eukaryotic cells have thousands of tiny mitochondrial genomes which support a massive nuclear genome

The total amount of DNA is similar in both, but the distribution is very different: eukaryotes have thousands of tiny mitochondrial genomes that support energetically a massive nuclear genome

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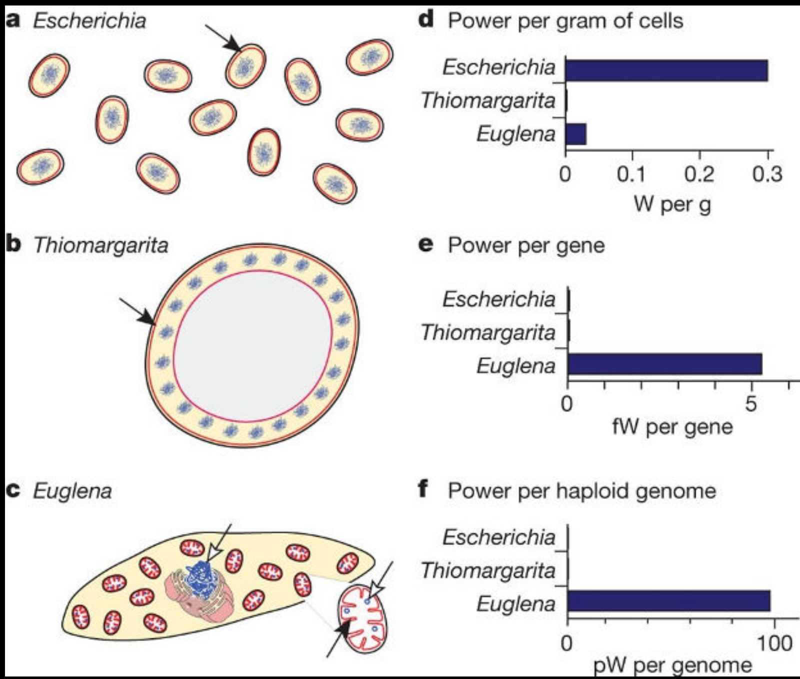
The genomic asymmetry in eukaryotes gives us ~5 orders of magnitude more energy for gene expression

We can have large genomes and make tens of thousands of times more protein from each gene



Lane N, Martin W. The energetics of genome complexity. *Nature*, 467: 929-934 (2010)

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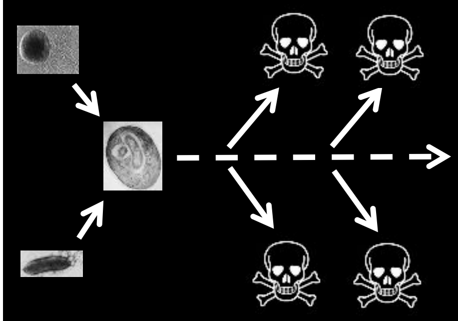
Why complex life only evolved once in 4 billion years



Endosymbioses between bacteria is rare – only one known example
Problem of living together – conflict resolution, coadaptation, etc

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An ‘evolutionary scandal’

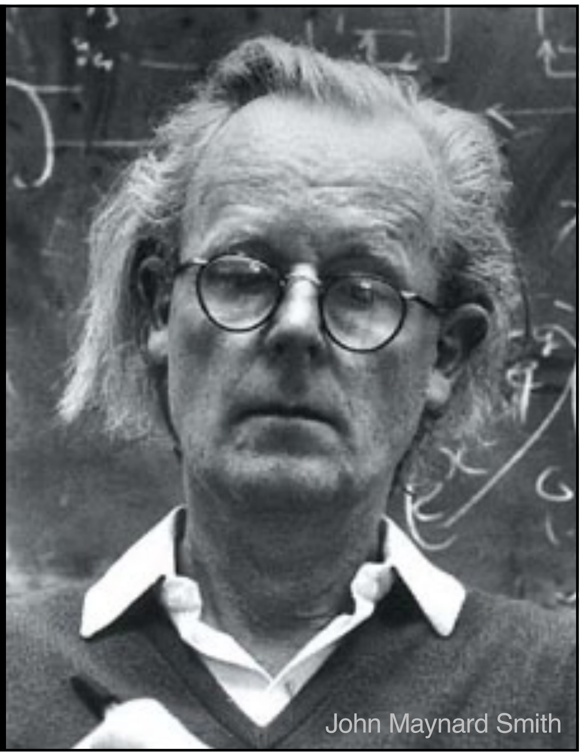
All complex life is made of eukaryotic cells

Eukaryotes are monophyletic, so by definition arose once in 4 billion years

All eukaryotes share universal traits e.g. the nucleus, ER, Golgi, dynamic cytoskeleton, mitochondria, membrane trafficking, mitosis, meiosis…

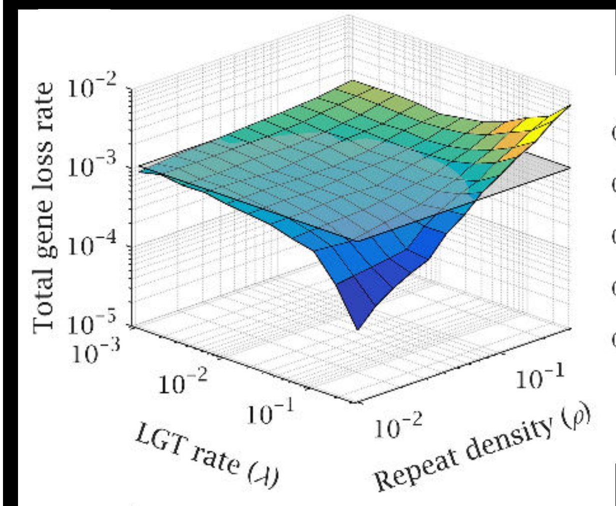
Bacteria do not evolve any of these morphological traits – why not?

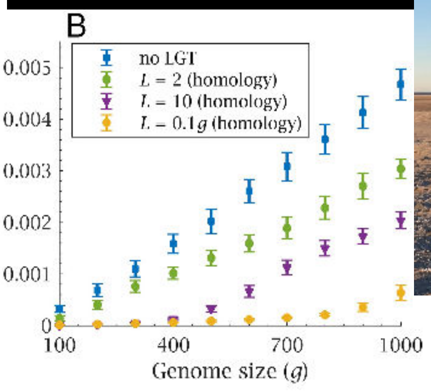
All eukaryotes have them all – why?


John Maynard Smith

23

Sex arose from LGT – enabled much larger genomes





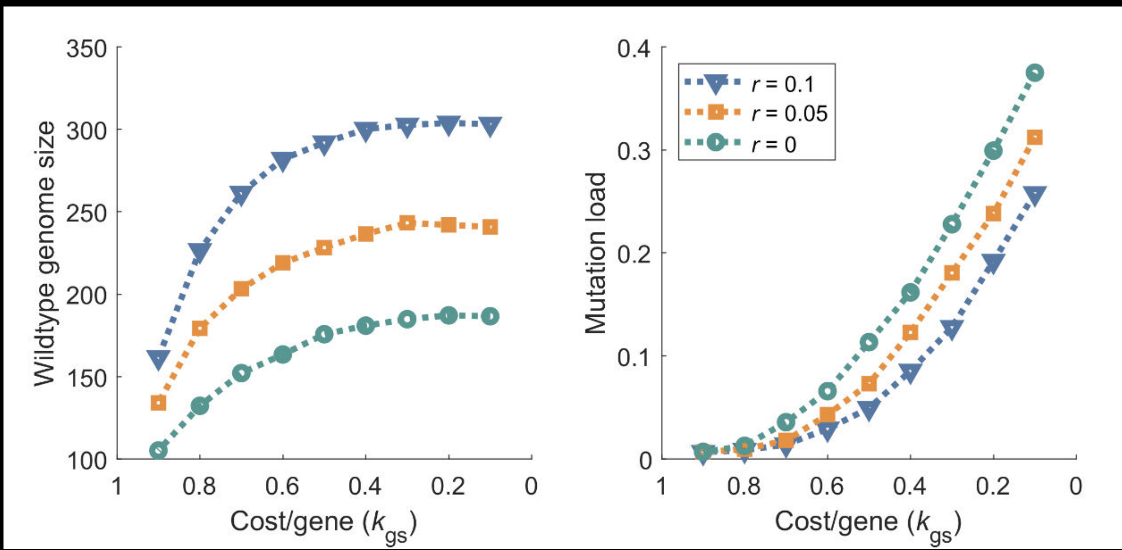

Marco Colnaghi

Frequent LGT with single genes can’t sustain large genome – need whole chromosomes

Colnaghi M, Lane N, Pomiankowski A. Repeat sequences limit the effectiveness of lateral gene transfer and favored the evolution of meiotic sex in early eukaryotes. *Proc Natl Acad Sci USA* 119: e2205041119 (2022).

24

Mitochondria AND sex are needed for large genomes



Mitochondria lower the cost per gene, but sex is needed to maintain WT genes

Colnaghi M, Lane N, Pomiankowski A. Two-step meiosis enables the expansion of early eukaryotic genomes. MS in preparation (2024).

25

Meiotic sex can maintain the quality of large eukaryote-sized nuclear genomes

Bacterial LGT cannot do this

But there is no obvious need for the two parents to be different sexes, especially in unicellular eukaryotes

Why are there two sexes?

Could two sexes select for mitochondrial genome quality?

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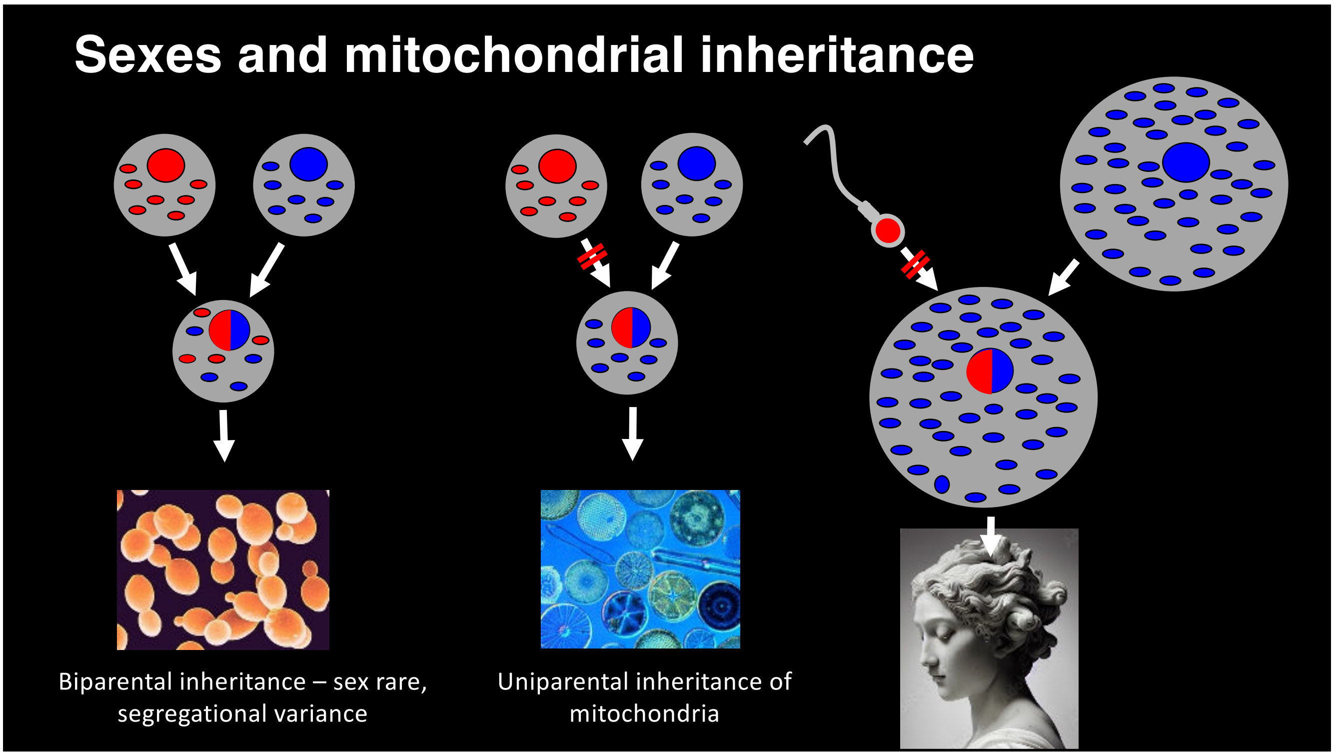
Sexes and mitochondrial inheritance
Biparental inheritance – sex rare, segregational variance
Uniparental inheritance of mitochondria

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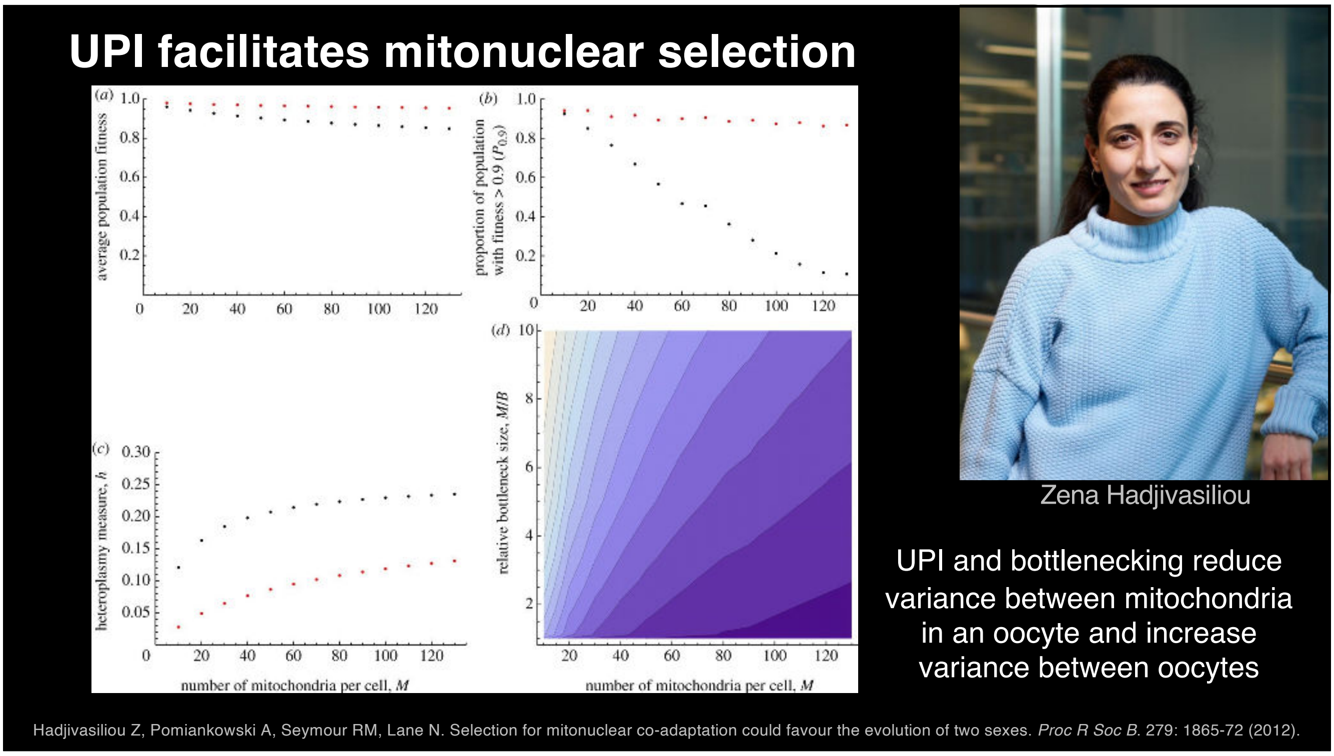
UPI facilitates mitonuclear selection
(a)
average population fitness
(b)
proportion of population with fitness > 0.9 ($P_{0.9}$)
(c)
heteroplasmy measure, h
number of mitochondria per cell, M
(d)
relative bottleneck size, M/B
number of mitochondria per cell, M
Zena Hadjivasiliou
UPI and bottlenecking reduce variance between mitochondria in an oocyte and increase variance between oocytes
Hadjivasiliou Z, Pomiankowski A, Seymour RM, Lane N. Selection for mitonuclear co-adaptation could favour the evolution of two sexes. *Proc R Soc B*. 279: 1865-72 (2012).

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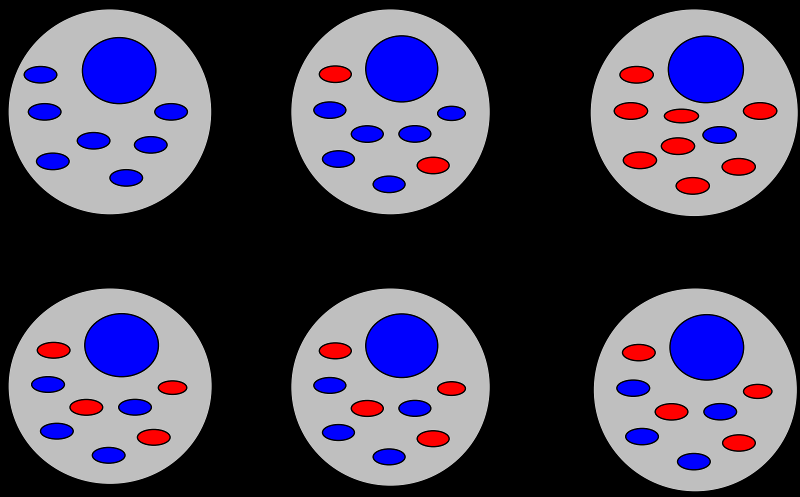
Uniparental inheritance increases variance

UPI + bottleneck generates clonal populations of mitochondria, good and bad

BPI generates heteroplasmic mitochondria, hard for selection to distinguish between



UPI increases variance between zygotes, facilitating selection and increasing fitness.

Sex increases variance between individuals in nuclear genes, two sexes increases variance in mtDNA

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Mother's curse

Maternal inheritance means mtDNA must be selected for female fitness

Nuclear background can compensate for female-optimized mtDNA in males

Male-harming mitochondrial SNPs can be unmasked by outcrossing

In isogenic animals, male fertility should vary with mtDNA as same nuclear background cannot compensate for all.

Flo Camus

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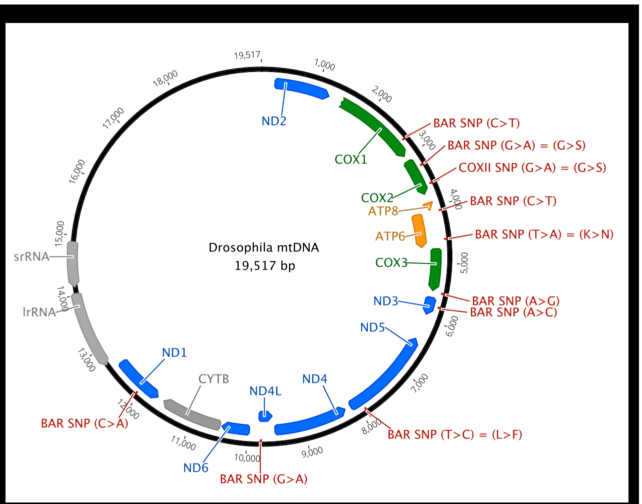

Drosophila is ideal experimental model: different mtDNA haplogroups can be set against isogenic nuclear background

Isonuclear background, three mtDNA haplotypes:

- WT (coevolved mtDNA)
- COX (1 SNP different in COXII)
- BAR (9 SNPs different in protein-coding genes)

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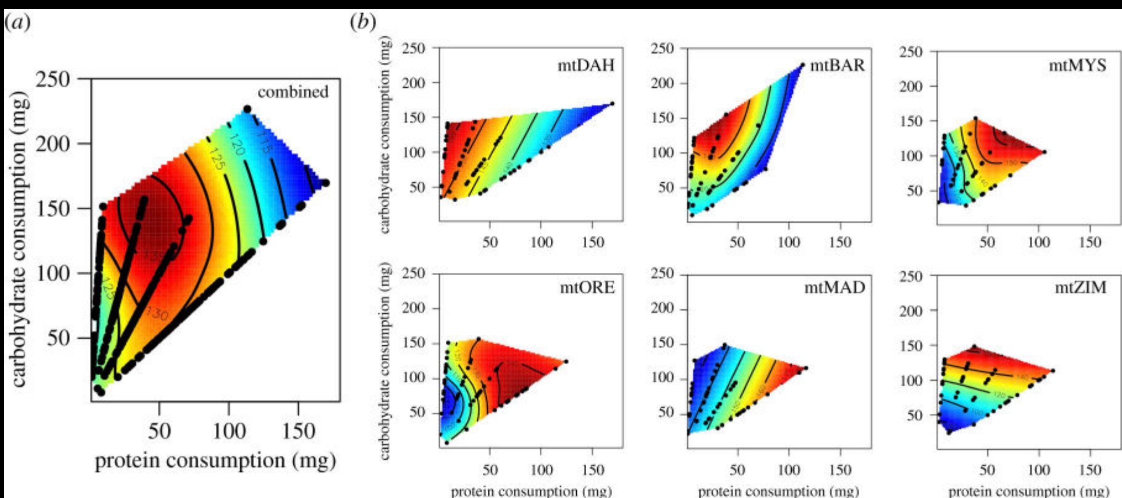
Male fitness varies with diet and mtDNA



Nutritional geometry for different mtDNA against isonuclear background

Optimal carbohydrate:protein varies from 1:1 to 4:1 depending on mitonuclear interactions

Camus MF, Moore J, Reuter M. Nutritional geometry of mitochondrial genetic effects on male fertility. *Biol Lett* 16: 20190891 (2020).

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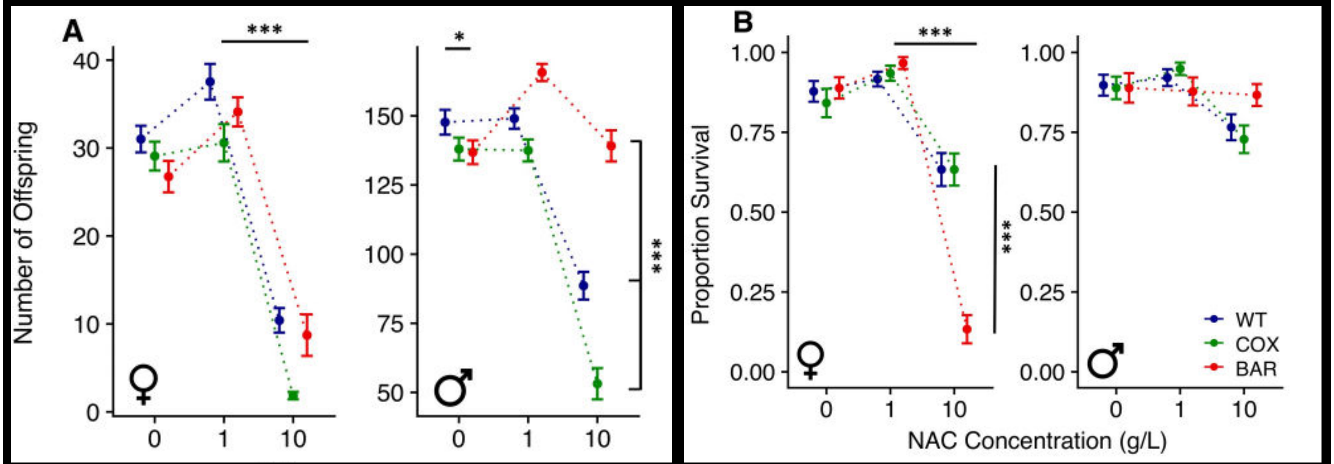
Can NAC improve male fertility? Yes, but it kills BAR females



80% BAR females but not males nor other lines died by day 12 on 10 mg/ml NAC

Camus MF, Rodriguez E, Kotiadis V, Carter H, Lane N Suppression of respiratory complex I by redox stress shortens lifespan in flies with mitonuclear incompatibilities. *J Exp Gerontol* **175:** 112158 (2023)

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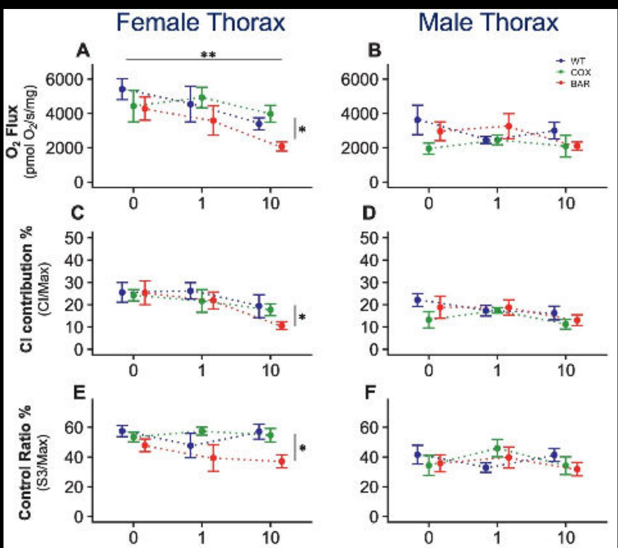
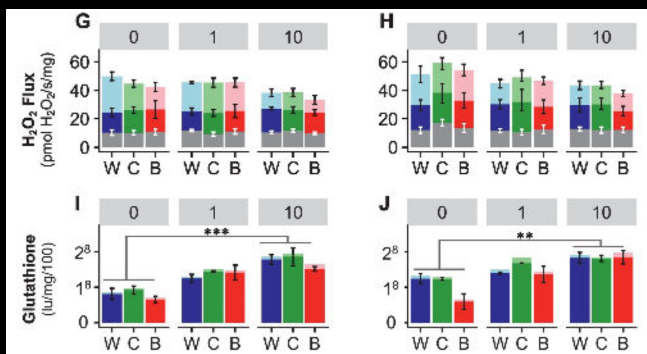
NAC suppresses complex I but does not alter ROS flux





Most ROS comes from complex I.

Flies limit ROS flux by suppressing their respiration to the point of death.

Camus MF, Rodriguez E, Kotiadis V, Carter H, Lane N Suppression of respiratory complex I by redox stress shortens lifespan in flies with mitonuclear incompatibilities. *J Exp Gerontol* **175:** 112158 (2023)

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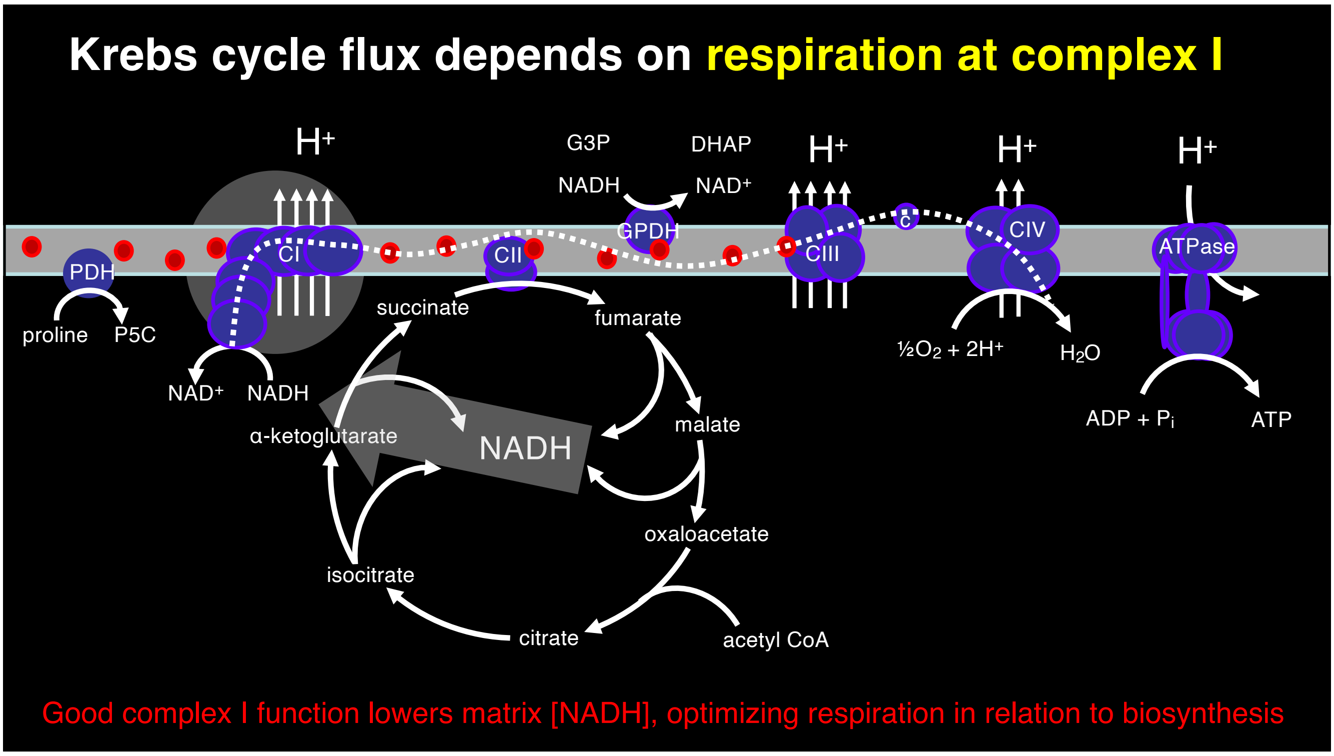
Krebs cycle flux depends on respiration at complex I
H+
G3P
DHAP
NADH
NAD+
H+
H+
H+
PDH
CI
CII
GPDH
c
CIII
CIV
ATPase
proline
P5C
succinate
fumarate
½O2 + 2H+
H2O
NAD+
NADH
malate
ADP + Pi
ATP
α-ketoglutarate
NADH
oxaloacetate
isocitrate
citrate
acetyl CoA
Good complex I function lowers matrix [NADH], optimizing respiration in relation to biosynthesis

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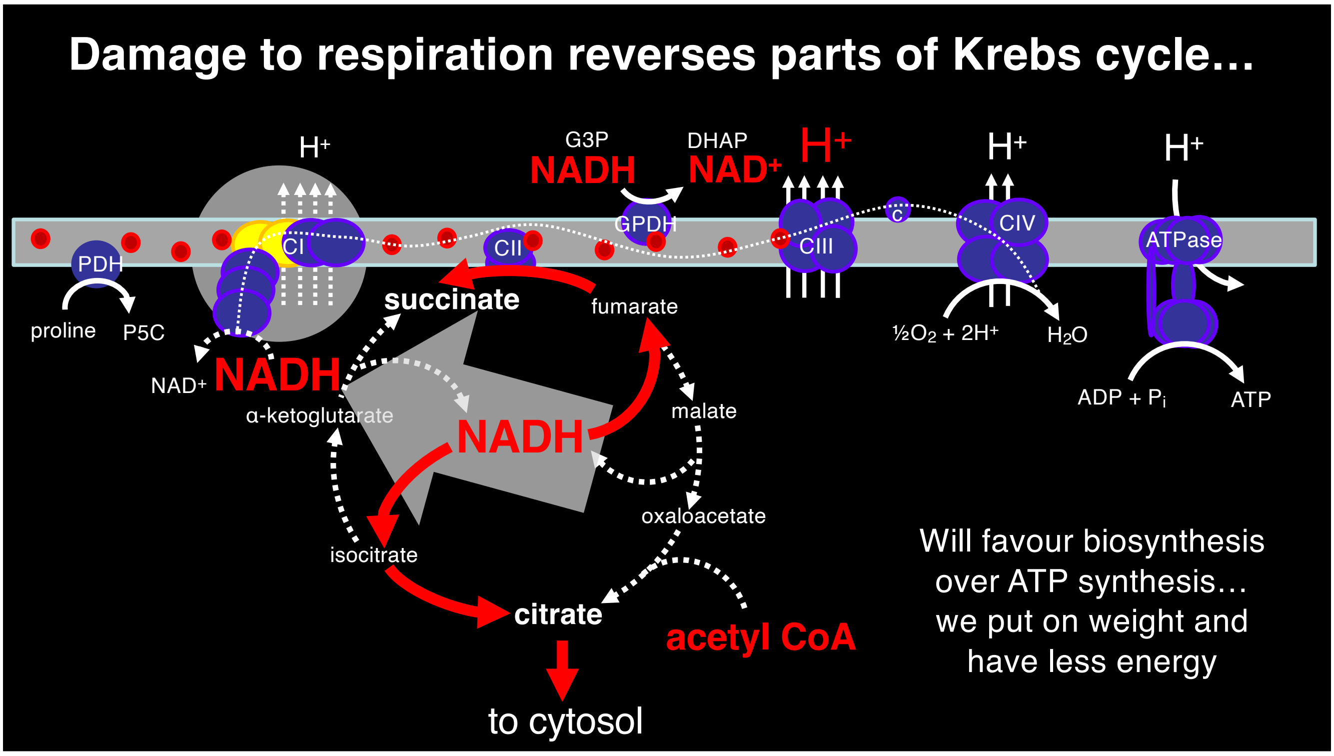
Damage to respiration reverses parts of Krebs cycle…
H+
G3P
NADH
DHAP
NAD+
H+
H+
H+
PDH
CI
CII
GPDH
c
CIII
CIV
ATPase
succinate
proline
P5C
fumarate
½O2 + 2H+
H2O
NAD+
NADH
α-ketoglutarate
malate
ADP + Pi
ATP
NADH
oxaloacetate
isocitrate
Will favour biosynthesis
over ATP synthesis…
we put on weight and
have less energy
citrate
acetyl CoA
to cytosol

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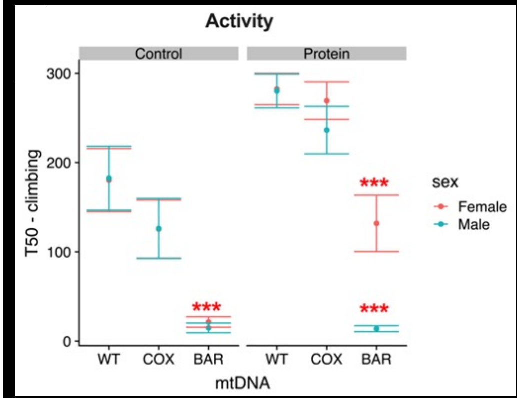
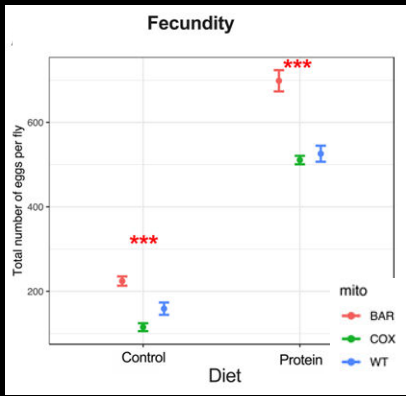
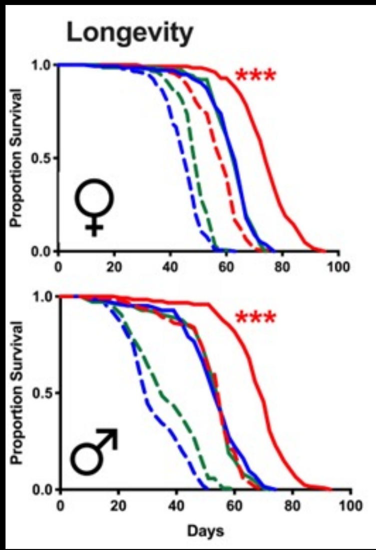
Unstressed BAR females are 'superflies'







Control vs high protein diet

BAR flies are more active, have greater fecundity, and are longer lived – an unusual evolutionary combination

Higher fitness from mismatched mitochondria is not what we expected

Rodriguez E, Inwongwan S, Camus F, Lane N. Mitonuclear interactions shape metabolic plasticity, fitness and longevity. MS in prep (2024).

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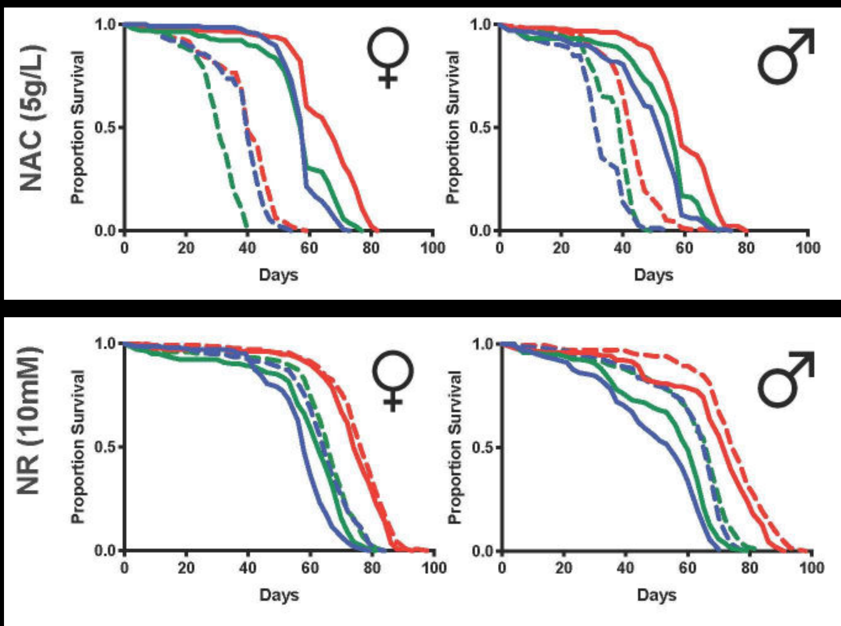
BAR females generally outperform other fly lines.



Lower doses of NAC less catastrophic to BAR females – BAR marginally longer lived than WT or BAR flies

Nicotinamide riboside (NR) supplementation increased lifespan – but less for BAR than WT or COX

Why do BAR females have high fitness despite mtDNA mismatch?

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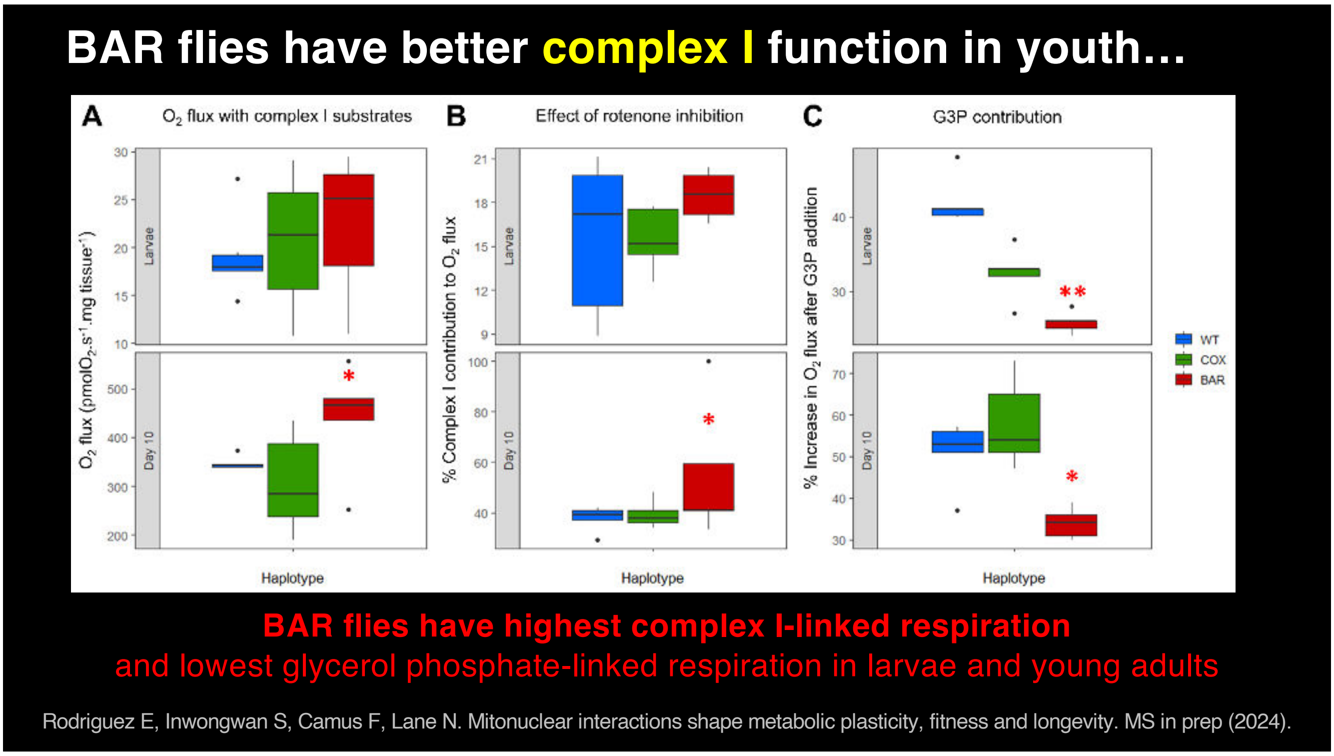
BAR flies have better complex I function in youth…
A
O2 flux with complex I substrates
B
Effect of rotenone inhibition
C
G3P contribution
O2 flux (pmolO2.s-1.mg tissue-1)
% Complex I contribution to O2 flux
% Increase in O2 flux after G3P addition
Larvae
Day 10
Haplotype
WT
COX
BAR
BAR flies have highest complex I-linked respiration
and lowest glycerol phosphate-linked respiration in larvae and young adults
Rodriguez E, Inwongwan S, Camus F, Lane N. Mitonuclear interactions shape metabolic plasticity, fitness and longevity. MS in prep (2024).

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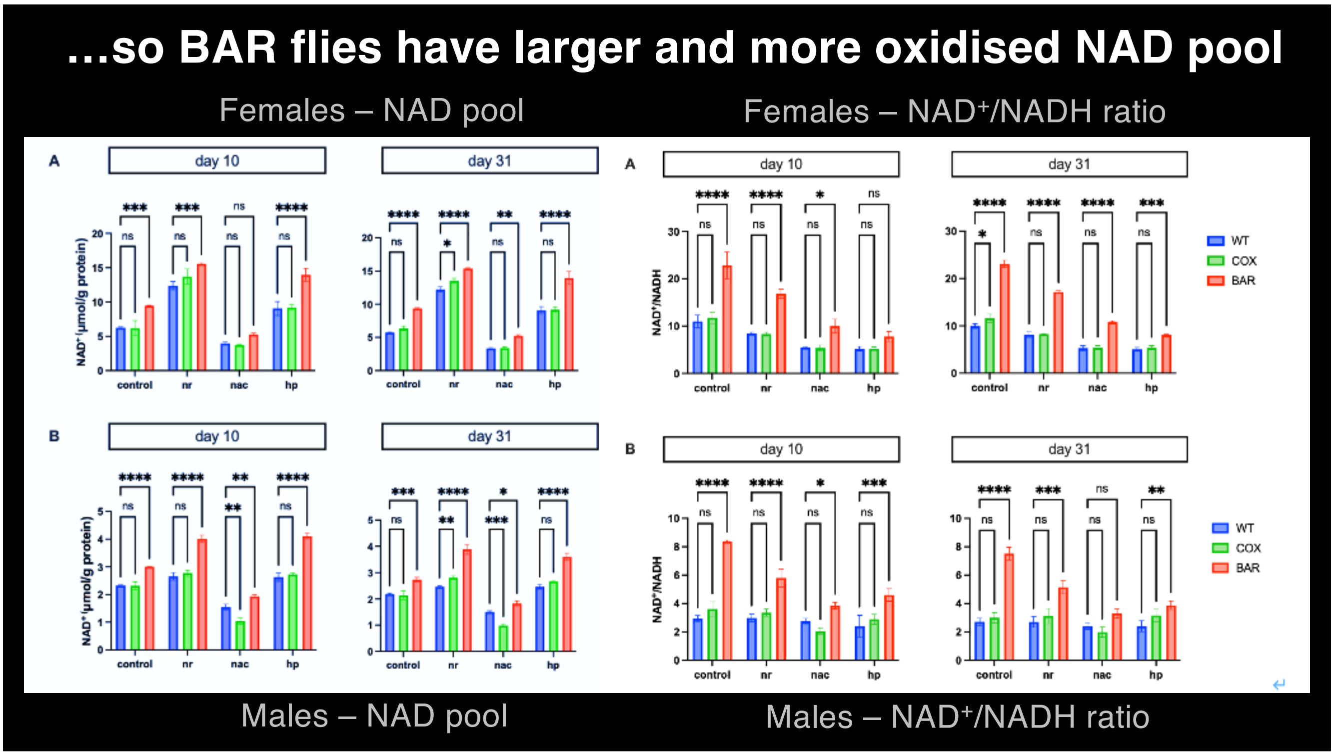
…so BAR flies have larger and more oxidised NAD pool
Females – NAD pool
Females – NAD+/NADH ratio
A
B
day 10
day 31
NAD+ (µmol/g protein)
NAD+/NADH
control
nr
nac
hp
WT
COX
BAR
Males – NAD pool
Males – NAD+/NADH ratio

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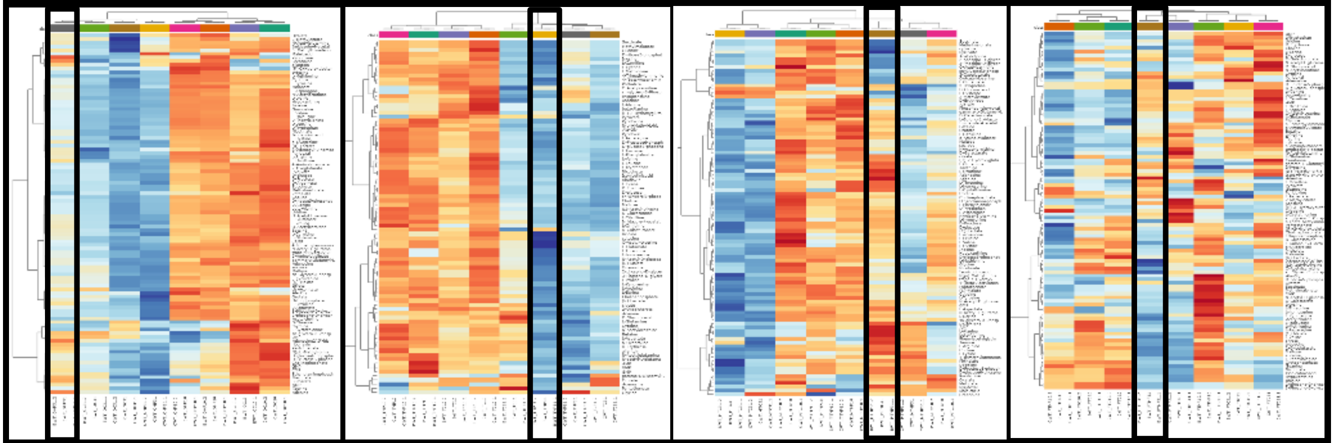
Metabolomics – big differences between fly lines

Ovaries | Testes | Male thorax | Female thorax



Small differences in respiration between fly lines over time and with HP diet produce big differences in $\log_{10}$ metabolite concentrations, but hard to recognize meaningful patterns

Rodriguez E, Inwongwan S, Camus F, Lane N. Mitonuclear interactions shape metabolic plasticity, fitness and longevity. MS in prep (2024).

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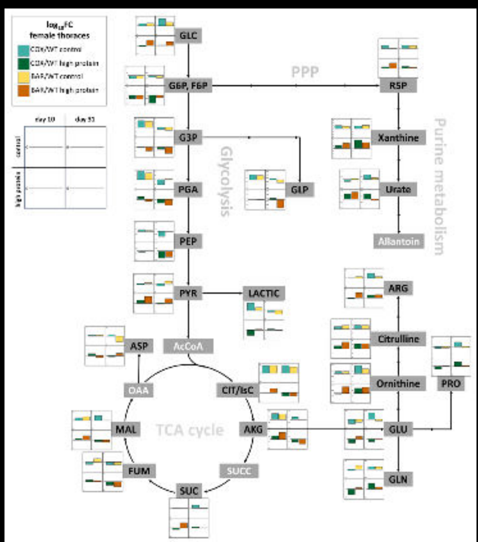
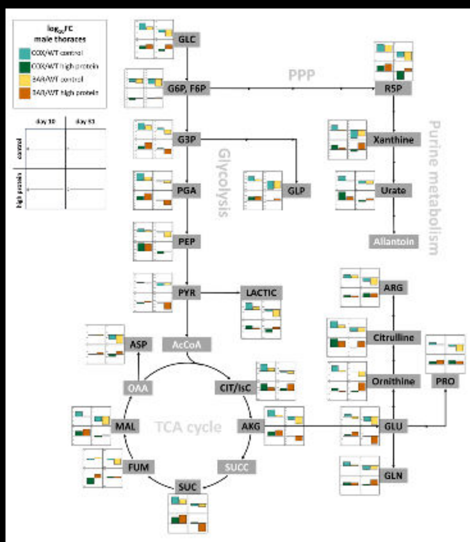
Central metabolism – changes in metabolites vs WT





The mitonuclear mismatched fly lines COX and BAR mostly behave in a similar way relative to WT

Rodriguez E, Inwongwan S, Camus F, Lane N. Mitonuclear interactions shape metabolic plasticity, fitness and longevity. MS in prep (2024).

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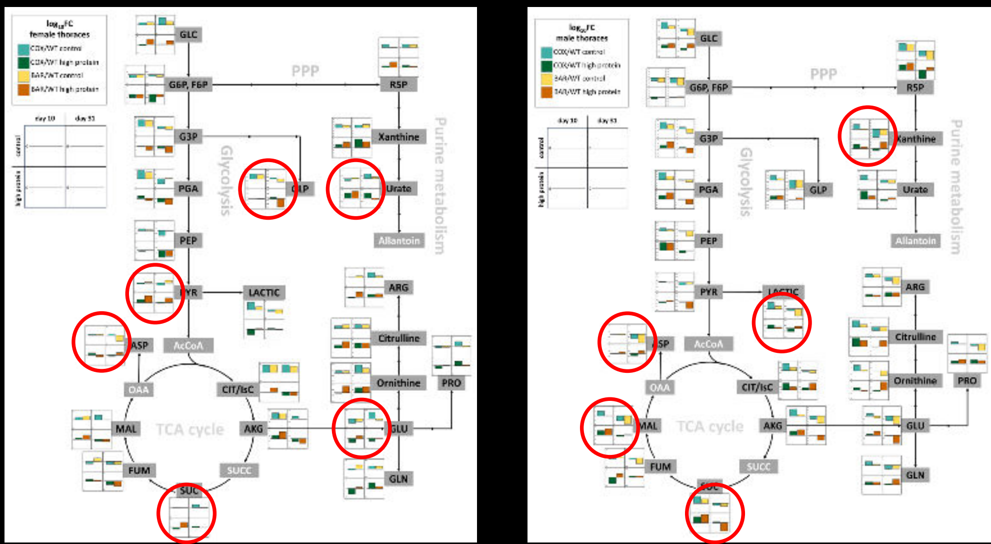
Central metabolism – changes in metabolites vs WT



But the inflection points are metabolically significant – malate-aspartate shuttle, succinate, glycolysis, glycerol phosphate input, nitrogen loss – BAR maintain better complex I activity

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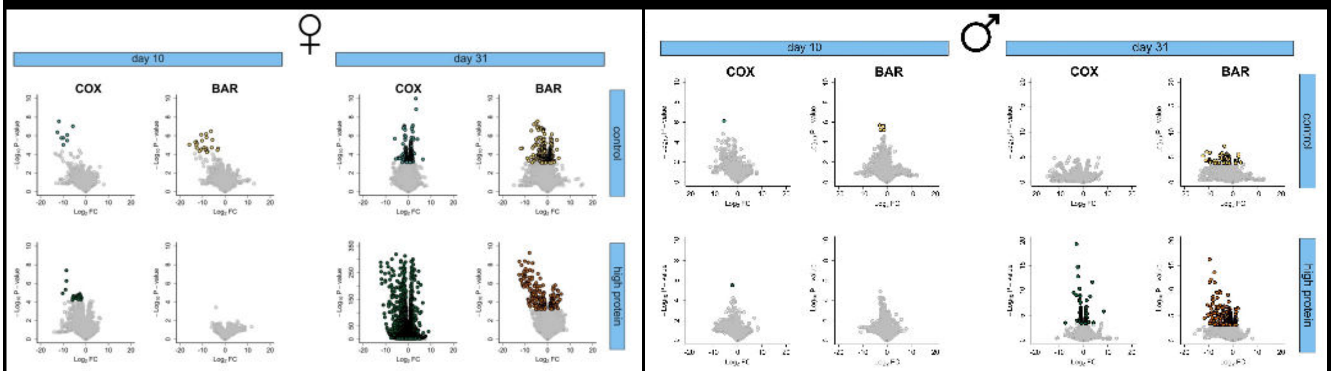
Overall changes in gene expression vs WT



Log 2-fold change in gene expression – X axis shows fold-change
Y axis shows significance (depends in part on quality of replicates).

BAR flies show larger changes in gene expression than COX vs WT including both down- and up-regulation – greater metabolic plasticity

Rodriguez E, Inwongwan S, Camus F, Lane N. Mitonuclear interactions shape metabolic plasticity, fitness and longevity. MS in prep (2024).

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Membrane bioenergetics drove metabolism at the origin of life

The acquisition of mitochondria enabled the evolution of complex life on Earth – the eukaryotic cell, sex and two sexes

Maternal inheritance of mtDNA leads to **Mother's curse** – selection for mtDNA against nuclear background is critical

Drosophila illustrates importance of mitonuclear interactions

Mitonuclear interactions shape metabolic plasticity, fitness, activity, longevity, and responses to nutrition and redox stress – big effects

Mitochondria central to nutritional medicine – everyone is different!

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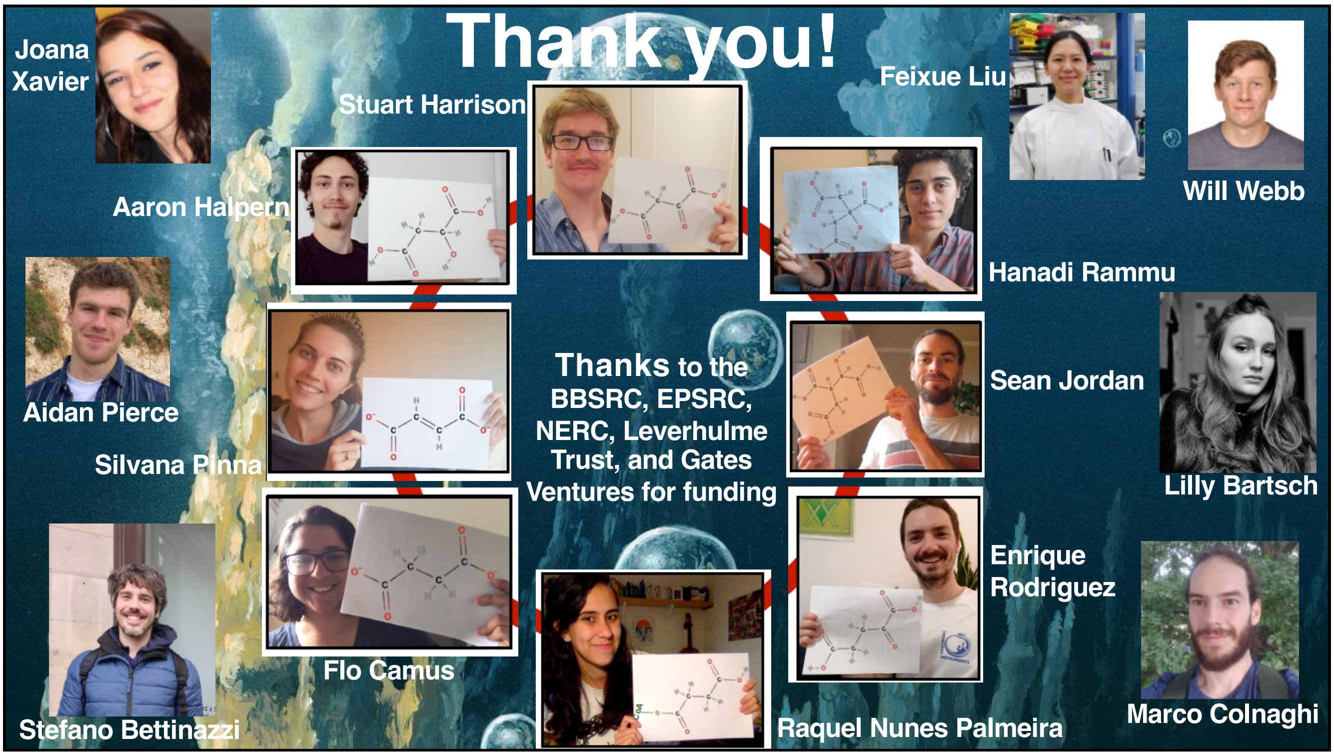
Thank you!
Joana Xavier
Stuart Harrison
Feixue Liu
Will Webb
Aaron Halpern
Hanadi Rammu
Aidan Pierce
Thanks to the BBSRC, EPSRC, NERC, Leverhulme Trust, and Gates Ventures for funding
Sean Jordan
Silvana Pinna
Lilly Bartsch
Enrique Rodriguez
Flo Camus
Stefano Bettinazzi
Raquel Nunes Palmeira
Marco Colnaghi

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NMI SUMMIT 2024
An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, & Healthy Ageing
Friday 11th October
Featuring Professor Nick Lane, Dr. Iain Hargreaves, Dr. Joseph Pizzorno, Dr. Nina Fuller-Shavel, Dr. Deanna Minich and Benjamin Brown
An event by:
Nutritional Medicine Institute
Platinum sponsors:
regenerus labs
pure encapsulations

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